REMARKS

The Present Invention

The present invention pertains to a dual specificity lymphocyte, compositions comprising the same, a pharmaceutical composition comprising the same, and a method of preparing the same.

The Pending Claims

Claims 1, 4, 7, 8, 10, 11, 40, 41, 44-61, and 71-82 are pending. Claims 1, 4, 7, 8, 10, 46, and 72-78 are directed to a composition comprising a dual specificity T lymphocyte. Claims 11 and 47-51 are directed to a dual specificity lymphocyte. Claims 40 and 52-56 are directed to a pharmaceutical composition comprising a dual specificity T lymphocyte. Claims 41 and 58-61 are directed to a method of preparing lymphocytes having dual specificity, while claim 71 is directed to the lymphocytes made therefrom. Claims 79-82 are directed to a composition comprising a population of T lymphocytes.

Discussion of the Amendments to the Claims

The amendments to the claims presented herein are the same as the claim amendments presented in the Amendment and Response to Final Office Action mailed on January 11, 2005, that have not yet been entered. Claim 1 has been amended to delete "recombinant T-cell receptor, either of" from part (i). This subject matter is now the subject of new claims 72-76. As noted below, this amendment obviates the concern expressed in the Office Action on page 10, first paragraph, in regards to the indefiniteness rejection. Additionally, the Office Action alleges that the claims may be inherently anticipated by the prior art. New claims 77-82 are directed to subject matter, which applicants believe cannot be inherently anticipated by the prior art. Claims 77-82 are supported in the specification by, for instance, page 31, line 4, of paragraph 81 through page 32, line 14, of paragraph 81. Claims 80 and 82 are further supported by paragraph 0053 on page 17. Moreover, the claims have also been amended as explicitly suggested by the Office Action on page 3, third complete paragraph. Specifically, claims 1, 11, 40, and 41 have been amended to recite "a cell that is allogeneic," as suggested by the Office. No new matter has been added by way of these amendments.

Request for Interview

In accordance with the Manual of Patent Examining Procedure (MPEP) 713.01, Applicants hereby request that a telephonic interview be held between the undersigned attorney and the Examiner to further discuss the rejections of the claims.

Discussion of the First Rejection Under 35 USC 112, First Paragraph

In point I beginning on page 3 of the final Office Action, the Office maintains the rejection of claims 1, 3, 4, 7, 8, 10, 11, 40, 41, and 44-61 and rejects claim 71 under 35 USC 112, first paragraph, as allegedly failing to comply with the written description requirement. This rejection is traversed for the reasons set forth below.

The Office contends that the scope of lymphocytes having a second receptor (namely, an endogenous T-cell receptor) that recognizes any cell that is allogeneic to the lymphocyte is new matter. As framed by the court in *In re Rasmussen*, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981), the concept of new matter is properly employed as a basis for objection to amendments to the abstract, specification or drawings attempting to add new disclosure to that originally presented. See also MPEP 2163.01. However, such T lymphocytes are supported by the originally presented specification at, for example, paragraph 42 on page 11, lines 3-6 of paragraph 53 on page 17, and original claims 1 and 2, in combination with the specification at page 11, lines 8-12. Specifically, paragraph 42 states: "'Dual specificity lymphocytes' as that phase is used herein refers to lymphocytes capable of reacting with both a tumor antigen and a pre-selected strong antigen. The tumor antigen reactivity may be conferred by genetically modifying lymphocytes with a chimeric T-cell receptor gene encoding a binding site for the tumor antigen. Tumor antigen reactivity may also be conferred by native TCR itself. Reactivity with the pre-selected strong antigen(s) is preferably conferred by *in vitro* expansion of the isolated population of lymphocytes by specific T-cell activation using one or more pre-selected strong antigens." Lines 3-6 of paragraph 53 on page 17 states: "In one embodiment, the specific expansion step amplifies an individual or subpopulation of T-cell whose *endogenous TCR* is directed to the strong antigen(s) used to expand the T-cells." (emphasis added) Original claims 1, 2, and 11 read as follows:

> 1. A composition comprising a preselected population of lymphocytes having a chimeric receptor or T-cell receptor reactive with a tumor antigen and *an endogenous receptor reactive with a preselected strong antigen.* (emphasis added)

2. The composition of claim 1, wherein the strong antigen is an allogeneic agent.

11. A lymphocyte having a T-cell receptor reactive with an allogeneic agent and a chimeric receptor reactive with a tumor antigen.

The specification describes allogeneic agents on page 11, lines 8-12, as antigens derived from genetically non-identical members of the same species, and lists allogeneic tissues, cells, proteins, peptides, nucleic acids as examples thereof.

While other support for these claims can be found in the application, these teachings of the instant specification alone are enough to demonstrate that the subject matter is not new matter.

Although Applicants have previously pointed to Examples 3-9 and 11 as support for the rejected subject matter, the Office maintains that support for the subject matter cannot be found in the specification, and that Examples 3-9 and 11 only teach stimulating the cells with PBMC and determining if the cells recognize allogeneic PBMC.

As discussed above, lymphocytes having an endogenous receptor reactive with a cell that is allogeneic to the lymphocyte is not new matter. In addition to the above-recited parts of the originally-filed application, Examples 3, 5, and 9 provide support for the claimed lymphocytes having an endogenous receptor reactive with a splenocyte, B cell, dendritic cell, or PBMC that is allogeneic to the lymphocyte .

Example 3, inclusive of Figures 3A and 3B, provides a proof-of-principle experiment, wherein the number of Thy 1.1 T-cells was remarkably increased when the recipient mice received an immunization with allogeneic splenocytes or dendritic cells (DCs) (black bars), in contrast to the mice that did not receive the splenocyte or DC immunization (white bars). As one of ordinary skill in the art recognizes, T cell proliferation, which is evidenced by an increase in cell number, is a hallmark of T cell stimulation, in which the T cell receptor binds to and reacts with the antigen. As stated in paragraph 2 of the Declaration of Dr. Patrick Hwu, the increased numbers of the Thy 1.1 T-cells shows that the endogenous T-cell receptors reacted to the allogeneic splenocytes or DCs.

Also, Example 5 discloses dual specificity T-cells having a receptor which is reactive to allogeneic splenocytes (page 30, line 3, of paragraph 79) and a chimeric receptor reactive to a tumor antigen, Folate Binding Protein (FBP) (page 30, line 2 of paragraph 79). Example 9 discloses cells having a receptor which is reactive to one of allogeneic PBMC, B cells, and dendritic cells (page 35, line 8, of paragraph 83) and a chimeric receptor (Mov-γ) (page 35, line 11 of paragraph 83). In this regard, the specification supports lymphocytes comprising

an endogenous T-cell receptor reactive with a cell that is allogeneic to the lymphocyte. Accordingly, the rejected claims do not comprise new matter.

The Office maintains that a T lymphocyte comprising an Mov-γ receptor and an endogenous receptor reactive with an allogeneic splenocyte, dendritic cell, B cell or peripheral blood cell is new matter, since support allegedly cannot be found in the specification. The Office specifically alleges that page 30, paragraph 79 of Example 5 does not show reaction with allogeneic splenocytes and, thus, does not show that the T-cells had an endogenous T-cell receptor reactive with the splenocytes. Although the specification does not explicitly demonstrate reaction with allogeneic splenocytes, the reaction is implicit to the teachings of the instant specification, such that one of ordinary skill in the art would conclude that the T-cells described in Example 5 had such an endogenous T-cells receptor. Because the specification states that the T-cells were "dual specificity allogeneic/Mov-γ T-cells" and that mice injected with these cells were immunized with allogeneic splenocytes (page 30, paragraph 79 of Example 5), one of ordinary skill in the art would conclude that the dual specificity T-cells had an endogenous receptor reactive with an allogeneic splenocyte.

Furthermore, Figure 5 demonstrates that the tumor-bearing mice injected with both allogeneic splenocytes and dual specificity T-cells became tumor-free. As stated in paragraph 3 of the Declaration of Dr. Patrick Hwu, the fact that the tumor-bearing mice became tumor-free under these conditions shows that the allogeneic splenocytes reacted with the endogenous T-cell receptors of the dual specificity T-cells, thereby causing the dual specificity T-cells to clonally expand in the mice, which, in turn, allowed the mice to become tumor-free. Therefore, given the explicit and implicit teachings of Example 5, T lymphocytes comprising an Mov-γ receptor and an endogenous receptor reactive with an allogeneic splenocyte is not new matter.

The Office further contends that the specification at page 35, paragraph 83 of Example 9 does not teach that PBMC had an endogenous T-cell receptor reactive with the allogeneic splenocytes, PBMC, B-cells, or dendritic cells. As stated in paragraph 4 of the Declaration of Dr. Patrick Hwu, the increased number of PBMC responder cells, which were T-cells, shows that the endogenous T-cell receptor of the responder T-cells reacted with the allogeneic PBMC, dendritic cells, or B cells. Therefore, the cells described in paragraph 83 were lymphocytes comprising a chimeric receptor reactive with a tumor antigen (Mov-γ) and an endogenous receptor reactive with a cell that is allogeneic to the lymphocyte. Thus, dual specificity T lymphocytes as claimed are in fact described in the specification, and accordingly, the subject matter is not new matter.

The Office further argues on page 4 of the final Office Action that "[t]he specification does not teach the [endogenous] receptor will recognize any allogeneic cell as broadly claimed." Applicants traverse this rejection. To comply with the written description requirement of 35 USC 112, paragraph 1, each claim limitation must be expressly, implicitly, or inherently supported by the originally filed disclosure. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species. See also MPEP 2163.05. In the instant case, the specification discloses several examples of dual specificity T lymphocytes having an endogenous receptor reactive to a variety of allogeneic cells. As discussed in depth above, the specification teaches dual specificity T lymphocytes having an endogenous receptor reactive with allogeneic splenocytes (Examples 3 and 5), PBMC, dendritic cells, or B cells (Example 9). Accordingly, the instant specification adequately supports the instant claims, such that written description requirement is met.

In view of the foregoing, lymphocytes comprising an endogenous receptor reactive with an allogeneic splenocyte, PBMC, dendritic cell, or B cell is not new matter. Furthermore, the claims are adequately described by the originally-filed specification. Therefore, Applicants respectfully request that the first rejection under Section 112, first paragraph, of claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61, and 71 be withdrawn.

Discussion of the Second Rejection Under 35 USC 112, First Paragraph

In point II beginning on page 5 of the final Office Action, the Office maintains the rejection of claims 1, 3, 4, 7, 8, 10, 11, 40, 41, and 44-61 and rejects claim 71 under 35 USC 112, first paragraph, as allegedly lacking adequate written description. Specifically, the Office contends that the "chimeric receptor reactive with a tumor antigen" does not meet the written description requirements, because the instant specification does not disclose the alleged required DNA sequences of all the chimeric receptors encompassed within the scope of the claim. This rejection is traversed for the reason set forth below.

First, the ordinarily skilled artisan would, upon reading the specification, conclude that Applicants were in possession of the claimed invention. At least for this reason, the application contains an ample written description of the claimed invention.

Second, as noted by the MPEP 2163, the description need only describe in detail that which is new or not conventional. See *Hybritech v. Monoclonal Antibodies*, 802 F.2d at 1384, 231 USPQ at 94; *Fonar Corp. v. General Electric, Co.*, 107 F.3d at 1549, 41 USPQ2d at 1805. In the instant case, chimeric receptors reactive with a tumor antigen were known in the art at the time of filing the subject patent application. Darcy et al., *J Immunology* 164:

3705 (2000), which is attached hereto, states: "Several single chain variable domain (scFv) receptors reactive to [tumor-associated antigens] on ovarian, breast, and colon carcinoma have been functionally expressed in mouse T cell lines such as MD45 and in both mouse and human lymphocytes." Specific chimeric receptors known in the art at the time of filing the instant application include a chimeric receptor reactive to a tumor antigen expressed in colon carcinoma (Haynes et al., *J Immunol* (January 2001) 166: 182-187 (article attached hereto)), a chimeric receptor reactive to a tumor antigen expressed in breast cancer (Dakappagari et al., *Cancer Res* (July 15, 2000) 60: 3782-3789 (article attached hereto)), and chimeric receptors reactive to a renal cell carcinoma antigen (Weijtens et al., *J Immunol* (July 15, 1996) 157: 836-843 (article attached hereto), Weijtens et al., *Gene Ther* (September 1998) 5: 1195-1203 (abstract attached hereto), and Weijtens et al. *Int J Cancer* (July 17, 1998) 77: 181-187 (abstract attached hereto)). The DNA sequences encoding the parts of these chimeric receptors were also known in the art at the time of filing the instant application. For instance, GenBank Accession Numbers D13555, S52322, and U88067 disclose DNA sequences encoding the T cell receptor zeta chain, the V_H region of the anti-carcinoembryonic antigen (anti-CEA) antibody, and the single chain Fv fragment of the anti-CEA 79 antibody, respectively (GenBank records attached hereto). Accordingly, because such chimeric receptors were known in the art at the time of filing the instant application, and because the DNA sequences used to make such chimeric receptors also were known, the specification is not required to include DNA sequences of the chimeric receptors.

Furthermore, as stated on page 9 of the Amendment and Response to Office Action mailed on June 23, 2004, there is no basis for a *per se* rule requiring disclosure of complete DNA sequences when claiming DNA sequences, let alone when claiming cells that require DNA sequences for the production thereof (see the Office's Guidelines for Written Description Requirement, published in the Federal Register, Volume 66, No. 4, page 1101, Response to Comment 9 (January 5, 2001)).

In view of the foregoing, claims 1, 3, 4, 7, 8, 10, 11, 40, 41, 44-61 and 71 are adequately described. Therefore, Applicants request that the rejection for lack of written description be withdrawn.

Discussion of the Rejection Under 35 USC 112, Second Paragraph

The Office Action maintains the rejection of claims 1, 3, 4, 7, 8, 10, 11, 40, 41, and 44-61 and rejects claim 71 under Section 112, second paragraph, as allegedly indefinite. Specifically, the Office alleges that the phrase "recombinant chimeric receptor" or "recombinant T-cell receptor" in the context of claim 1 does not make sense. Applicants

thank the Examiner for helping to ensure that the pending claims are clear. To obviate the rejection, applicants have separated the claim terms at issue into separate claims. In view of the amendments to the claims (i.e., cancellation of "recombinant T-cell receptor" from claim 1, and the addition of new claim 72) this rejection does not apply to the claims as pending.

Discussion of the Rejections Under 35 USC 102

The Office Action maintains the rejection of claims 1, 3, 4, 7, 8, 10, 11, 40, 41, and 44-61 and rejects claim 71 under 35 USC 102 (e) as being anticipated by U.S. Patent 5,830,755 (the '755 patent). Also, claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58, and 61 remain rejected under Section 102 (e) as allegedly anticipated by U.S. Patent 6,407,221 (the '221 patent). Claims 1, 3, 7, 8, 11, 40, 41, 45-67, 50, 52, 56, 58, and 61 remain rejected and claim 71 is rejected under Section 102 (e) as allegedly anticipated by U.S. Patent 5, 359,046 (the '046 patent). These rejections are traversed for the reasons set forth below.

The Office interprets the '755 patent in three different ways. In a first interpretation, the Office relies upon the data of Table 8 of the '755 patent to support that the TIL have an endogenous T-cell receptor reactive with a cell that is allogeneic to the T-cell. Specifically, the Office argues that even non-transduced cells (TIL NV) produced cytokine in response to exposure to murine sarcoma cells (24JK cells), such that transduced TIL would have both a chimeric receptor that recognizes a tumor antigen and an endogenous T-cell receptor reactive with an allogeneic cell. However, as stated in paragraph 5 of the Declaration of Dr. Patrick Hwu, the 24JK cells are not allogeneic to the TIL. Rather, the cells are syngeneic to each other.

Furthermore, the Office interprets the term "allogeneic" based upon the first definition found in Dorland's Medical Dictionary, which states:

"**allogeneic** 1. having cell types that are antigenically distinct. 2. in transplantation biology, denoting individuals (or tissues) that are of the same species but antigenically distinct, as opposed to syngeneic and xenogeneic".

However, "allogeneic" can also be defined as "being genetically different although belonging to or obtained from the same species" (see The American Heritage® Dictionary of the English Language, Fourth Edition Copyright © 2004, 2000 by Houghton Mifflin Company.), "taken from different individuals of the same species" (see http://hyperdictionary.com/medical/allogeneic, Copyright © 2000-2003, Webnox Corp.; and http://www.cancer.gov), or "variation in alleles among members of the same species" (see the Genomics Glossary of the Genome Atlantic website at http://www.genomeatlantic.ca/glossary.php?alpha=A).

Although there are several definitions for the term "allogeneic," the teachings of the specification make it clear which definitions are appropriate with respect to the present invention. For instance, on page 11, the specification states the following: "Allogeneic agents or 'alloantigens' are antigens derived from genetically non-identical members of the same species. Allogeneic tissues, cells, proteins, peptides, nucleic acids and/or other cellular components may be used to select an individual or subpopulation of lymphocytes." In light of this teaching of the specification, it is clear that the phrase "cell that is allogeneic to the lymphocyte" refers to a cell derived from a genetically non-identical member of the same species. That is, the term "allogeneic" as used in the claims does not refer to just *any* matter that is antigenically distinct. Rather, this term refers to antigens derived from genetically non-identical members of the same species. In view of the foregoing, the '755 patent does not anticipate the claimed invention under the Office's first interpretation.

Moreover, it appears that the Office misinterprets the term "allogeneic" as meaning "antigenically distinct" and opposed to "*having* cell types that are antigenically distinct." This is evident from the Final Office Action on page 12, line 3 of the first complete paragraph, at which the Office has underlined "antigenically distinct" when citing the first definition of Dorland's Medical Dictionary definition. Also, the Office states on page 12, lines 4-6 of the first complete paragraph: "JK24 cells are 'antigenically distinct' to the transduced TIL because they have low expression of MHC Class I molecules as compared to claon 4JK." Therefore, it appears that the Office's interpretation of the term "allogeneic" is in error.

In a second interpretation of the '755 patent, the Office contends that the endogenous T-cell receptor that reacts to a cell that is allogeneic to the T-cell is inherent to the TIL disclosed in the '755 patent, since a population of TIL has a diverse array of endogenous T-cell receptors, such that one of the many endogenous T-cell receptors present in the population of transduced TIL must recognize at least one allogeneic cell. This speculation, however, is not supported by evidence. Under the principles of inherency, the prior art must necessarily function in accordance with the claims it allegedly anticipates. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 51 USPQ2d 1943 (Fed. Cir. 1999); *In re King*, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986). Inherency may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. *Continental Can Co. USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 20 USPQ2d 1746 (Fed. Cir. 1991) (emphasis in original). In the instant case, there is no evidence of record that demonstrates that the diversity of a TIL population guarantees that the population contains a T-cell having an endogenous T-cell receptor reactive to an allogeneic

cell. Accordingly, inherency cannot be demonstrated in the instant case. Therefore, the '755 patent does not anticipate the claimed invention under the Office's second interpretation.

In a third interpretation, the Office alleges that the '755 patent discloses TIL which are exposed to an antigen prior to transduction to stimulate growth and expansion of cells that recognize the antigen. However, the '755 patent does not disclose that the antigen is an allogeneic cell, such that the '755 patent does not disclose each and every element of the claims. Accordingly, the '755 patent does not anticipate the claimed invention under the Office's third interpretation.

The Office also rejects claim 41 as allegedly anticipated by the '755 patent, since the steps of the method of claim 41 are allegedly disclosed by the '755 patent. However, as stated above, the '755 patent does not disclose contacting lymphocytes with a cell that is allogeneic to the lymphocytes. Thus, the '755 patent does not disclose each and every element of the claims. Accordingly, the '755 patent cannot be said to anticipate the method of claim 41.

In the Advisory Action dated January 21, 2005, the Office contends that the Declaration of Dr. Hwu, which was filed with the Amendment and Response to Final Office Action mailed on January 11, 2005, ignores the definition of "allogeneic" found in Dorland's Medical Dictionary and also ignores the second interpretation of the anticipation rejection. The purpose of a declaration under 37 CFR 1.132 is to provide evidence to traverse a rejection or objection. However, there is no rule that the declaration needs to address each and every interpretation or point for a given rejection. In the instant case, the Declaration of Dr. Hwu is submitted to provide evidence that the teachings of Table 8 are contrary to what the Office asserts. The second interpretation of the anticipation rejection in view of the '755 patent and the definition of "allogeneic" is addressed without the need for a declaration under §1.132. Thus, the Office is requested to fully consider the Declaration of Dr. Patrick Hwu as regards the first interpretation of the anticipation rejection in view of the '755 patent.

In view of the foregoing, the '755 patent does not anticipate the instantly claimed invention. Therefore, Applicants respectfully request that the rejection under Section 102 in view of the '755 patent be withdrawn.

The Office Action alleges that the '221 and '046 patents anticipate claims 1, 3, 7, 8, 11, 40, 41, 45-47, 50, 52, 56, 58, 61, and 71. Specifically, the Office Action alleges that the '221 and '046 patents disclose T-cells transduced with a vector encoding a chimeric receptor that recognizes a tumor antigen. In some instances, the tumor antigen allegedly is the HIV protein gp120. The Office further alleges that the T-cells of the '221 and '046 patents inherently comprise an endogenous T-cell receptor, which is reactive to an allogeneic cell,

since the T-cells were in a diverse population of T-cells. The rejection of the claims under Section 102 in view of the '221 patent is traversed for the reasons set forth below.

The Office alleges that the HIV gp120 protein is considered as a tumor antigen because the protein was caused to be expressed in a tumor cell. However, "tumor antigen" is defined in the instant application on page 13, lines 8-15 of paragraph 0046, as a molecule that can be used to target therapy against a tumor and includes those antigens only found on tumor cells (i.e., tumor specific), those which are expressed on tumor cells and on limited normal tissues, and those which are over-expressed on tumor cells compared to the expression on a wide variety of normal tissues (i.e., over-expressed antigens). Also, the specification at page 13, lines 15-18, lists several examples of over-expressed tumor antigens, all of which are known to be over-expressed on a tumor *in vivo* and, unlike the gp120 protein of the '221 patent, are not *caused to be expressed* by a tumor cell. Therefore, because the gp120 protein is not a molecule that can be used to target therapy against a tumor *in vivo*, this protein cannot be considered as a tumor antigen as defined by the instant application.

Even if the gp120 protein could be considered as a tumor antigen, which it cannot, the TIL do not have an endogenous T-cell receptor reactive with a cell that is allogeneic to the lymphocyte.

The Office alleges that the T-cells of the '221 patent inherently comprise the endogenous receptor which reacts to an allogeneic cell. As noted above with respect to the '755 patent, there is no evidence of record that a diverse population of T-cells have an endogenous T-cell receptor reactive to an allogeneic cell. Accordingly, inherent anticipation of the claimed invention has not been demonstrated in the instant case. That is, even assuming for the sake of argument, that the '221 and '046 patents may disclose T-cells having a receptor that reacts to a tumor antigen, neither patent explicitly or even inherently disclose T-cells having a second endogenous receptor that reacts to a cell that is allogeneic to the T-cell. Thus, neither the '221 patent nor the '046 patent disclose each and every limitation of the claims. Accordingly, neither the '221 patent nor the '046 patent can be said to anticipate the claims. In view of the foregoing, Applicants respectfully request that the rejection under § 102 in view of the '221 and '046 patents be withdrawn.

Conclusion

The application is considered in good and proper form for allowance, and the Examiner is respectfully requested to pass this application to issue. If, in the opinion of the

Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney.

Respectfully submitted,

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